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Dementia (E McDade, Section Editor)

Treatment of Primary Progressive Aphasia

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Opinion statement

Primary progressive aphasia (PPA) is a neurodegenerative disease that primarily affects language functions and often begins in the fifth or sixth decade of life. The devastating effects on work and home life call for the investigation of treatment alternatives. In this paper, we present a review of the literature on treatment approaches for this neurodegenerative disease. We also present new data from two intervention studies we have conducted, a behavioral one and a neuromodulatory one using transcranial direct current stimulation (tDCS) combined with written production intervention. We show that speech-language intervention improves language outcomes in individuals with PPA, and especially in the short term, tDCS augments generalization and maintenance of positive language outcomes. We also outline current issues and challenges in intervention approaches in PPA.

Introduction

Primary progressive aphasia (PPA) is a neurodegenerative syndrome that mainly affects language abilities, including word finding, word usage, word comprehension, and sentence construction [1•, 2•, 3•]. PPA is characterized by insidious onset and gradual deterioration of language associated with atrophy of the frontal and temporal regions of the left hemisphere [1•, 4]. In this neurodegenerative condition,

language is disproportionately impaired for at least 2 years, without impairment in other cognitive domains other than praxis [5•]. PPA is comprised of three main variants, each with specific clinical features and pathophysiology: non-fluent agrammatic PPA, semantic variant PPA, and logogpenic variant PPA [3•, 6]. Difficulty naming is an early and persistent impairment common to all three variants of PPA [7•, 8, 9].

Non-fluent agrammatic PPA (nfaPPA) is characterized by core features of agrammatic language production and/or apraxia of speech [10, 11•, 12]. Spoken modality-specific naming impairments are reported in nfaPPA [13] as are naming deficits specific to impaired naming of actions rather than objects [13, 14•, 15]. Individuals with nfaPPA may become mute early in their disease progression [16] and develop clinical features of parkinsonism and related syndromes, such as corticobasal syndrome or progressive supranuclear palsy [17]. Imaging abnormalities are present in left posterior frontal and insular regions [10, 18, 19]. The pathology is typically a tau-opathy, such as corticobasal degeneration, progressive supranuclear palsy, or frontotemporal lobar degeneration-tau [3•].

Semantic variant (svPPA) is defined by marked anomia and single-word comprehension deficits across input and output modalities [20]. Individuals with svPPA may display progressively impaired object naming, with preserved naming of actions, and greater difficulty in the written versus spoken modality, although both modalities are compromised [14•, 15]. This variant is associated with atrophy in ventrolateral anterior temporal lobes bilaterally, usually greater atrophy on the left [10, 19]. Speech fluency, syntax, and word repetition are relatively preserved [10]. Individuals with svPPA also manifest behavioral symptoms as their disease progresses [21, 22]. The pathology is most often frontotemporal lobar degeneration-TDP-43 [3•].

Logopenic variant (lvPPA) is distinguished by word retrieval and phrase and sentence repetition deficits. Single-word comprehension and speech articulation are relatively spared [3•, 23•]. Generalized cognitive decline, including language abilities, attention, memory, and visuospatial skills, is manifested over time [24]. Imaging abnormalities are seen in the left temporoparietal junction [10, 19]. The pathology is usually Alzheimer's disease [3•].

Due to its onset in middle age, PPA profoundly impacts work and home life. Behavioral interventions—mainly for spoken naming—have been described to remediate the language deficits in PPA [25–27, 28••, 29••]. Word production impairments (both in oral and written modalities as manifested in deficits in picture naming and spelling) have important clinical value in PPA since they are the two earliest symptoms, thus allowing for early detection and intervention. Word finding and fluency difficulties are among the first symptoms in logopenic (lvPPA) and non-fluent (nfaPPA) variants [30]. Spelling is also impaired early in every subtype and may predict the PPA subtype early in the course of the disease [31•]. For example, surface dysgraphia symptoms are usually found in semantic variant (svPPA) or lvPPA but more rarely in nfaPPA. Those with nfaPPA sometimes rely on spelling when they eventually become mute [3•].

Cognitive mechanisms underlying spoken and written word production and implications for therapy

In this section, we review the cognitive mechanisms involved in spoken and written production since spelling, naming, and reading deficits are among the first and most disruptive symptoms in PPA, and their remediation is the goal of most interventions. Figure 1 shows the close relationship between spoken and written word production mechanisms in models of cognitive architecture. Specifically, word representations in either the written or spoken modality may be accessed from the other modality or the semantic (word meaning) system [32, 33]. The implication, which is the basis of several treatment studies in post-stroke aphasia [34, 35], is that both lexical and sublexical routes from one modality may contribute to word retrieval in the other. Thus, behavioral treatments stimulating residual knowledge across the semantic, phonological, and orthographic domains have resulted in cross-domain improvements [36–39]. For example, a combination of spelling treatment with spoken repetition [37, 40, 41] improved written and spoken production even in participants with semantic impairments.

Spoken and written production intervention studies in PPA

Intervention studies in PPA are, in general, difficult due to the degenerative nature of the disease, the variable rate of decline among individuals and the inherent heterogeneity of each variant. For example, individuals with

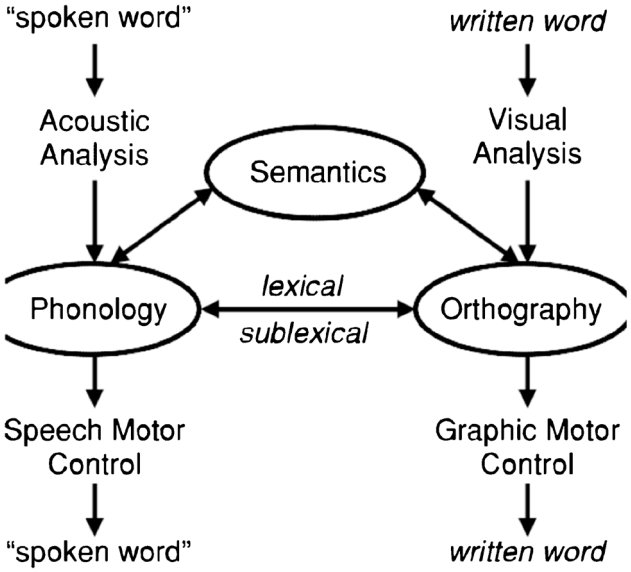

Fig. 1. Interactive model of lexical processing.

nfaPPA decline more rapidly in action than object naming, while those with svPPA show the opposite pattern [42•], and those with svPPA show most notable decline in object semantics [43, 44]. Therefore, most intervention studies are case reports or include a small number of participants (for a review, see [45••]). Behavioral studies—across all PPA subtypes—have mostly investigated treatment of word retrieval: (a) svPPA [46••, 47••, 48••, 49••, 50], (b) nfaPPA [51••, 52, 53], and (c) lvPPA [28••, 54••, 55••]. These studies have shown encouraging results of language therapy, i.e., potential for new lexical learning in svPPA [56••] and lvPPA [28••], benefit of implementing errorless strategies [50], the importance of early intervention [56••], and potential for generalizability and retention of therapy gains [25, 28••]. Long-term effects of therapy gains are either not systematically examined or outcomes were variable when examined. For example, Meyer and colleagues [57] reported response to repetition and reading/writing therapy for anomia in four individuals with PPA. They found significant improvements in some but not all treatment conditions over 5 months.

Different approaches may be used to address the naming impairment, or anomia, common in primary progressive aphasia. Graham et al. [46••] used repeated practice of names paired with pictures or descriptions of targeted items. Jokel et al. [48••] advocated errorless learning in their treatment paradigm in which pictures and spoken descriptions of items were provided, and the patient was instructed to attempt to name the target only if he was certain of the accuracy of his response. This errorless learning strategy was used successfully in subsequent treatment studies [49••, 50]. Beeson et al. [25] employed generative naming, in which individuals name members in categories under a time constraint in an intensive regime of 2-h treatment sessions, 6 days/week for 2 weeks, along with approximately 1 h of daily homework. Similarly, Henry et al. [56••] employed a rigorous therapy conducted once daily for 90 min, for a total of 12 treatment sessions over 16 days to improve lexical retrieval in the context of generative naming. In the treatment study by Meyer et al. [57], repetition and writing tasks, as well as forced-choice recognition, were used. In the repetition treatment, participants viewed a picture and a string of symbols and repeated the picture label after a spoken presentation. In the writing treatment, participants viewed a picture and its corresponding printed label, and then copied the label. In both treatments, a forced-choice recognition task was used to ensure that participants attended to both the pictures and the words. This therapy facilitates naming by accessing phonology via the non-semantic or orthography route. Thus, there is an evidence base that a variety of methods are effective in facilitating naming performance. Speech-language pathologists must consider this evidence as well as individual patient needs, degree of deficit, and cognitive models of language processing when planning treatment [45••].

Intervention studies in individuals with apraxia of speech (AOS) associated with nfaPPA, characterized by syntactic disorders and apraxia of speech (AOS) in the initial stages, have targeted the single-word level. A recent study used reading of multisyllabic words as an intervention strategy in PPA with lasting and generalizable results [58].

Only two behavioral studies of which we are aware have examined treatment of written language in PPA—one treating sublexical mechanisms [29••] and the other treating lexical processes [28••]. Both treatments were successful, but long-term follow-up was examined only in one study [28••] and was successful only for treated items. These studies have shown that results with language therapy alone are encouraging although limited, either because they have not shown generalization to untrained items or because they have lacked follow-up to evaluate the sustainability of therapy gains.

Transcranial direct current stimulation to augmenting language interventions

Transcranial direct current stimulation (tDCS) has been identified as a promising intervention to augment behavioral treatment benefits in language therapy programs, mostly in stroke [59••, 60••, 61••] and Alzheimer's disease (AD) [62••, 63••, 64]. The benefits of tDCS—its low expense, high safety profile, and non-invasive nature—justify research on its use in PPA as a possible means to augment behavioral intervention effects and reduce the rate of decline in language. The precise mechanisms of tDCS are unknown; however, it is thought that tDCS changes the membrane potentials of neurons in a relatively focal area of brain tissue under the skull [65••, 66, 67]. Anodal stimulation increases the likelihood of neural firing [67]. tDCS induces a subthreshold polarization of neurons too weak to generate action potentials, but sufficient to modulate the neuronal response threshold. Thus, tDCS alters the spontaneous firing rate of neurons to modulate their response to afferent signals [68]. These changes in response threshold correlate with task performance. Thus, increases or decreases in cortical excitability induced by tDCS are believed to promote long-term potentiation (LTP) and long-term depression (LTD). The changes in brain networks may include recruitment of undamaged areas of the brain to assume functions of damaged areas during language tasks [69, 70••].

The positive effects of tDCS in motor and higher cognitive functions—including language—have been identified in studies of healthy controls. After a single tDCS session, participants experienced improved performance lasting up to 5 h; however, long-lasting effects of tDCS have been documented only in studies with repeated consecutive tDCS sessions [61••, 71, 72••, 73]. Besides these proof-of-concept studies of healthy controls' motor skill learning, there is a recent proof-of-concept study of verbal word learning [74, 75••, 76] confirming memory formation and consolidation after repeated consecutive sessions. The clinical importance of tDCS requires establishing therapy generalization and maintenance of treatment in clinical populations. Two research groups have provided relevant evidence: Fridriksson's group in spoken naming remediation in post-stroke aphasia [61••, 77••] and Boggio's group in associative memory remediation in AD [78••, 79••, 80••]. After five consecutive stimulations, therapy gains were found to last up to 4 weeks [64, 78••, 79••, 80••]. The brain mechanisms that induce such effects are thought to be late long-term potentiation and/or protein synthesis [71, 72••, 73, 74], which may constitute the physiological basis of long-term memory formation and offline consolidation. Given that long-lasting learning reflects synaptic connectivity changes, the effects of tDCS are expected to be manifested in connectivity changes between nodes of neural networks. Indeed, studies that have looked at effects of tDCS on functional connectivity using resting-state fMRI (rsfMRI) have found significant changes in healthy controls [81–85].

tDCS interventions in neurodegenerative disease

tDCS has been shown to enhance cortical excitability and function [86, 87••, 88] when anodal current is applied in healthy individuals. Tasks employed in these studies include fluency, interference, picture naming, verbal learning, and proper noun learning. In clinical populations, tDCS has been used mainly to improve motor and language recovery, primarily after stroke [60••, 61••, 62••, 86, 88, 89••, 90, 91••, 92••, 93••, 94]. A wide range of tasks have been targeted in post-stroke aphasia, including verb naming [91••], auditory verbal working memory [86], repetition of syllables, and words for treatment of speech apraxia [94], word retrieval, or picture naming for anomia treatment [62••, 72••, 81, 90, 94–96]. Despite the plethora of reports on language recovery using tDCS after stroke, only a few studies have examined it in neurodegenerative diseases: three studies on AD [64, 80••, 97••], including only one study in which tDCS was applied for more than one session (five sessions) [80••] and which showed greater improvement with tDCS vs. sham in a visual recognition task (9 vs. 2.6 %) but without any task performed during either tDCS or sham conditions, two studies on frontotemporal dementia (FTD) [98••, 99••] (one session only with no effect of tDCS [98••] but also no task practiced during treatment, and ten sessions with more improvement over tDCS vs. sham [99••] coupled with an oral naming task), and ours in PPA [100••] where (after 15 treatment sessions coupled with a spelling task) we found greater improvement with tDCS vs. sham (35 % of patients made significant improvement on untrained words with tDCS vs. 16 % of patients made significant improvement on untrained words with sham). The tasks used in the tDCS studies were verbal and visual recognition memory in AD, spoken verbal fluency and naming in FTD, and spelling in our study in PPA. In the visual recognition memory task used in tDCS interventions in AD, two items (drawings of animals, persons and objects) were displayed on a computer screen for 10 s and then, 1 s later patients were shown a single picture and were asked to say whether the picture (test trial) had been presented before. The naming task used in the other FTD study [99••]

comprised a picture naming task of black and white drawings of objects displayed on a computer screen. There were two balanced lists of pictures, treated and untreated stimuli that were further split and practiced in each week of treatment (2 weeks of treatment overall). Items were specifically tailored for each patient and practiced for 25 min during anodal tDCS or sham. Treatment included several steps to elicit the oral production of a target noun: repetition of the target word, oral picture naming, and reading of the target word. In our spelling study in PPA, we used a similar treatment protocol: two sets of ten letters and corresponding words (starting with the same grapheme) were selected as trained and untrained items, respectively. Different sets of letter-word correspondences were practiced in each period (sham or tDCS). Participants were randomized in either sham or anodal tDCS for the first period in a within-subject cross-over design. Each period lasted 3 weeks, thus they received tDCS or sham for 15 consecutive sessions. In each trial, participants were given a sound to which they had to find the corresponding letter and were asked to write a word starting from it. Written production of the target word was induced by repetition, reading, studying, and copying. Less-impaired participants were also encouraged to produce as many words as they could.

One FTD study [98••] did not find any effect of tDCS in improving verbal fluency which may have been because there was only one 40-min stimulation session that was not coupled with language therapy. In this study, spoken verbal fluency was used as a measurement but not as treatment. Other studies that did not couple tDCS with language therapy have repeatedly yielded no improvement in both healthy and patient populations [101–103]. A highly consistent finding across studies using a wide array of tasks is that tDCS-induced facilitation is highly dependent on the task subjects perform during stimulation and that tDCS-only conditions are consistently unsuccessful [101–105].

We are aware of only three other neuromodulation studies in PPA; all three used repetitive transcranial magnetic stimulation (rTMS) [106, 107••, 108••], and all showed improvement with neuromodulation during language therapy tasks. Of particular interest is Trebbastoni et al.'s case study [107••] in which after TMS stimulation during five consecutive sessions twice (interleaved with five sham stimulations) over the dorsolateral prefrontal cortex and close to the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG), the PPA participant showed improvement in phonemic verbal fluency and written language (decrease of semantic and syntactic errors in sentences).

Long-term benefits of neuromodulation (tDCS or TMS) have not been clearly identified; this is especially true for neurodegenerative diseases. One study in AD showed improvement in naming one month after tDCS [78••]. In general, long-term effects—whenever shown—appeared after at least five consecutive days of stimulation. Determining the duration of therapeutic effects is critical, especially in neural degeneration, because it enables more effective planning of whether and when treatment should be repeated. In both recent studies using tDCS in PPA [99••, 100••], long-term effects (up to two months) have been identified, offering promise of the proposed intervention as a tool of slowing down the rate of decline in neurodegeneration.

Generalization of treatment gains to other language and cognitive functions

In addition to generalization to untrained items, generalization to untrained tasks is expected, and sometimes observed when trained and untrained tasks share cognitive functions [34, 35]. Two studies in post-stroke aphasia evaluated tDCS effects of training oral naming [96] and syllable-word repetition [89••] and have shown generalization to written naming. In published interventions in PPA, these effects are not fully investigated. Future studies should test the hypothesis that gains from training both spoken and written word representations will generalize to related language and cognitive functions. Furthermore, since language and cognitive impairments associated with PPA interfere with activities in daily life and life satisfaction, future studies should evaluate how improvements in language and cognitive functions enhance quality of life for individuals with PPA and their families.

Medications

Because the most common pathology underlying lvPPA is Alzheimer's disease pathology, the decline in symptoms might be reduced with cholinesterase inhibitors and/or memantine, medications that have been shown to somewhat reduce the rate of decline in cognition in clinically diagnosed Alzheimer's disease. However, a large randomized clinical trial specifically in lvPPA has not been completed. Case studies have reported improvement in language with steroid treatment [109] or Omentum Transposition Therapy [110], but these effects have not been replicated. Theoretically, medications that enhance neuroplasticity, such as selective serotonin reuptake inhibitors, might augment the effects of tDCS, but the combination of interventions has not been studied in PPA.

Conclusions: challenges and new venues

The present review shows that language interventions are possible and can be successful in a neurodegenerative disease. All behavioral interventions in PPA cited above showed improvement of the language function targeted. However, not all of them showed generalizable and long-lasting effects. Many reasons may be responsible for these findings: heterogeneity of symptoms and pathologies reflected by the different PPA variants, different stages of disease progression at baseline, and variable rate of decline between participants and studies. Neuromodulation with tDCS offers promise as a means of augmenting language therapy to improve written language function at least temporarily in PPA. The consistent finding of generalization of treatment benefits to untreated items and the superior sustainability of treatment effects with tDCS justifies further investigations. To date, there are only a few studies with small sample sizes, so results require caution in interpretation but offer hope for improved outcomes of combined language therapy and tDCS. Future interventions need to address particular challenges, such as ways to account for the variable effect of degeneration in each individual, generalization of treatment to other cognitive functions, and impact and improvement in quality of life of the individuals with PPA. Longitudinal studies also need to determine whether interventions have the potential of altering the rate of disease progression or even slowing down the progression of symptoms for some time. Future research is needed to determine whether medications, used alone or in combination with speech and language treatment with or without neuromodulation, can be of benefit in reducing the rate of language decline in PPA. Finally, future research should address the brain mechanisms involved in both behavioral and neuromodulatory interventions.

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Compliance with Ethics Guidelines

Conflict of Interest
Donna C. Tippett, Argye E. Hillis, and Kyrana Tsapkini declare no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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